NeST

Neoadjuvant Systemic Therapy in Breast Cancer

A national prospective multicentre audit of neoadjuvant systemic therapy in breast cancer

The NeST Steering Group

On behalf of

The Mammary Fold Academic Committee

And

The Northern Ireland Surgical Research Collaborative

Study Protocol v1.0

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1. Background

1.1. Neoadjuvant systemic therapy

Neoadjuvant systemic therapy (NST) is an established treatment strategy for early breast cancer. Multiple randomised controlled trials have demonstrated that systemic chemotherapy has equal efficacy in both the adjuvant and neoadjuvant settings [1, 2]. Use of NST provides early, effective systemic treatment, while carrying the advantage of potentially down-staging the primary tumour and enabling breast conserving surgery. Meta-analysis has shown this to be a safe approach, with acceptable local recurrence rates [3]. In addition to this, the use of NST incorporates the potential for clinicians to assess tumour sensitivity to treatment. Indeed, pathological complete response (pCR) to chemotherapy has been shown to be a good prognostic factor, with patients achieving pCR having significantly fewer distant recurrences at 5 years [4]. The rate of pathological complete response differs between disease subtypes; however, with the advent of targeted treatments (such as dual anti-HER2 therapies), pCR may be over 50% in HER2-positive breast cancer [5-7]. Neoadjuvant endocrine therapy is also a recognised treatment strategy [8], and indeed, data suggests that in strongly hormone receptor positive breast cancer, endocrine therapy may be as effective as chemotherapy in the neoadjuvant setting [9, 10].

In spite of evidence to support the safety and efficacy of NST, limited data is available on utilisation across the United Kingdom. Data from the UK Mastectomy Decisions Audit (MasDA) suggests that a significant proportion of patients underwent mastectomy as primary treatment, without consideration of NST. MasDA found that only 20% of women with ER positive disease and 40% of women with HER2+ tumours over 2cm were offered neoadjuvant treatment. Additionally, only 22% of patients with HER2 positive cancers undergoing mastectomy where the indication was 'large tumour to breast size ratio' were offered neoadjuvant treatment.

Furthermore, it is clear that increases in pCR rates have not translated into increasing rates of breast conserving surgery [11]. Evidence suggests that the use of NST does not significantly reduce the breast tissue volumes resected at surgery [12], and this is borne out by MasDA data confirming that a significant number of patients with a good response to NST proceeded to mastectomy. The reasons for this failure to leverage the potential surgical benefits of NST are unclear; it is possible that this reflects widespread surgical practice where the original tumour footprint is excised, rather than "response-adapted" surgery.

Finally, data suggesting that sentinel lymph node biopsy (SLNB) has an increased false negative rate following neoadjuvant chemotherapy [13] has resulted in variation in practice, with some units and surgeons undertaking SLNB after NST, and others carrying out ANC.

In conclusion, there is significant variation in practice in both the utilisation of NST in the UK, and in surgical decision-making around NST use. Furthermore, there is undoubtedly also significant variation in imaging practices and in terms of the use of pathological reporting systems for recording response to NST. There is a need to further explore current UK practice and use the data generated to define best practices and to support the development of future guidelines in this area.

1.2 Trainee research collaboratives

There are clearly challenges in carrying out large-scale, prospective, multicentre cohort studies. However, the trainee research collaborative model has been demonstrated to be both a time- and cost-effective method of carrying out both prospective audit and research studies in surgery [14, 15]. They have a proven track record in both the design and delivery of prospective cohort studies [16-18] and randomised clinical trials [19, 20] in general surgery. This model has also been successful in breast surgery, with both the iBRA (Implant Breast Reconstruction Evaluation study) [21] and the MasDA (Mastectomy Decisions Audit) showing that the methodology can be applied successfully in this setting.

The NeST (Neoadjuvant Systemic Therapy) study therefore aims to work with the Northern Ireland Surgical Research Collaborative, the Mammary Fold Academic Committee and the

existing trainee research collaborative networks to deliver first a survey of the national practices of NST, and subsequently a high-quality prospective audit of the practice and outcomes of NST across the UK.

2. Aims and Objectives

1. To establish current stated practice regarding the use of NST across the UK
2. To determine the current practice of NST, including
    a. Indications for use
    b. Treatment modalities in common use
    c. Monitoring of response to treatment
    d. Pathological reporting of response to NST
3. To explore surgical decision-making in the context of NST with respect to both the breast and axilla
4. To explore the use of further adjuvant therapies (radiotherapy and systemic therapies) following NST
5. To determine pathological response rates to NST in routine clinical practice
6. To establish best practice with regards to the use of NST, with a view to generating national guidelines

3. Definitions

3.1 Neoadjuvant systemic therapy

For the purpose of this study, neoadjuvant systemic therapy (NST) will be used to refer to all types of systemic therapy (chemotherapy, endocrine or biological/targeted therapies) used for definitive pre-surgical treatment of breast cancer. This will specifically exclude any patients being entered into “window of opportunity” studies where a short course of pre-surgical treatment is given in a research setting to test a biological hypothesis, as this is unlikely to be sufficient treatment to offer the opportunity of surgical downstaging

3.2 Pathological complete response

A variety of definitions of pathological complete response (pCR) to neoadjuvant systemic therapy have been reported. These include eradication of all tumour (in situ and invasive) from the breast and axillary nodes (ypT0 ypN0), eradication of invasive disease only from the breast and axillary nodes (ypT0/is ypN0) or eradication of invasive disease from the breast only (ypT0/is). A pooled analysis [22] confirmed that the first two of these definitions had stronger correlation with event-free and overall survival than did eradication of invasive disease from the breast alone. Therefore, for the purposes of this study, pCR will be defined as “no residual invasive disease in either breast or axillary lymph nodes”.

3.3 Clinical/radiological response

For the purposes of this study, clinical and radiological response will be considered as follows:

- Complete response - no evidence of residual disease on clinical examination or standard routine imaging
- Partial response - reduction in maximum tumour diameter on clinical examination or routine imaging
- Stable disease - no change in tumour size on examination or imaging
- Progressive disease - increase in maximum tumour diameter on examination or using imaging

4. Audit standards

There are currently no guidelines with regard to the use of neoadjuvant systemic therapy in breast cancer within the UK.

5. Methods

This is a trainee collaborative project which will be co-ordinated by the Mammary Fold Academic and Research Collaborative

The study will have two phases:

1. Exploration of current practice in the use of neoadjuvant systemic therapy in the UK by means of a questionnaire
2. Multicentre prospective audit of indications for, use of and outcomes of NST

Any breast unit providing NST as part of their routine management of breast cancer will be eligible to participate in this audit. Units will be invited to take part through the Association of Breast Surgery, the Mammary Fold, the Association of Surgeons in Training (ASiT) and the NCRI Breast Clinical Studies Group (CSG).

A local study lead, ideally a senior surgical trainee with an interest in breast surgery, or a senior medical oncology trainee with an interest in breast cancer, will be identified at each centre. In units where no trainee is attached, the unit lead can be any regular member of the surgical or oncology team. If the identified lead is a trainee, they will be required to identify a supervising consultant (either surgeon or oncologist) to act as the local Principal Investigator (PI) for the study. Unit leads/PIs will be responsible for obtaining the support of other team members, both surgical and oncological.

Support will also be sought from the professional associations, including the Association of Breast Surgery. We will ask that the ABS encourage all MDTs where NST is utilised to support their trainees in this audit.

5.1 Current practice questionnaire

Current practice in the utilisation of NST across the UK will be explored using an MDT questionnaire. The current practice questionnaire will be circulated to all local study leads, who will be responsible for administering the questionnaire at the MDT.

The aims of the current practice questionnaire are to:

1. Investigate variations in the use of NST across the UK
2. Explore the stated indications for the use of NST
3. Examine treatment regimens in common use, including the use of NET and NAC regimens
4. Investigate how clinical, radiological and pathological response to NST is assessed and reported across the UK
5. Assess stated surgical practice following NST, with respect to both primary breast and axillary surgery

5.2 Prospective audit

The second phase of the study will be a prospective clinical audit, co-ordinated by the individual unit leads as outlined above.

5.2.1 Logistical and governance issues

The unit lead will be responsible for registering their unit with the NeST study team (nestbcstudy@gmail.com), and for obtaining local audit approvals for the study. A copy of the local approval should be forwarded to the NeST study team prior to the start of data collection. If the unit lead is a trainee then the named supervising consultant will act as the local Principal Investigator for registration purposes. If the unit lead rotates out of the unit during the study period, then it will be their responsibility to nominate an incoming trainee to take on the role of unit lead.

Patient recruitment and data collection will be completed by the unit leads. It is anticipated that each unit lead will identify a small team of 2 - 3 people, including an oncology trainee, to help to conduct the audit locally. This includes liaising with the wider multidisciplinary team, including radiologists and pathologists, to ensure adequate data capture.

5.2.2 Patient inclusion and exclusion criteria

Inclusion criteria

- Age > 16 years
- Histologically confirmed diagnosis of breast cancer
- MDT recommended treatment of neoadjuvant systemic therapy (either hormonal or chemotherapy) - including patients entering into clinical trials of neoadjuvant systemic therapy.

Exclusion criteria

- Patients entering "window of opportunity" clinical trials

5.2.3 Patient identification and recruitment

It is expected that participating centres will recruit consecutive patients receiving neoadjuvant treatment into the audit. Potential participants will be identified by the local audit team via local MDTs, out-patient clinics, consultant surgeons and oncologists and clinical nurse specialists. Simple demographic, treatment and outcome data will be collected contemporaneously for each patient. Data will be anonymised using a unique alphanumeric study number, on a secure web-based database (REDCap) designed by Vanderbilt University [23, 24] (http://www.projectredcap.org/). Data regarding treatment, clinical/radiological response and surgical outcomes will be collected prospectively. Patients will be reviewed at their post-operative review visit to collect pathological response data. Note review will be performed to retrieve this data for patients who fail to attend this clinical follow-up appointment. Data will also be collected on women where neoadjuvant systemic therapy was recommended by the local MDT but declined by the patient, including reasons for declining treatment.

6. Data collection

The following datasets will be collected.

6.1 Current practice questionnaire

6.2 Prospective data collection questionnaire

The questionnaires comprising these two datasets are appended in Appendices A and B respectively.

7. Data validation and quality assurance

Following data collection, only data sets with >95% data completeness will be included in the analysis [25]. For quality assurance purposes, the local consultant Principal Investigator at selected sites will be asked to identify an independent person to verify a proportion of the submitted data. Overall, approximately 5% of all datasets will be independently validated. The independent assessors will be asked to review MDT records, Trust computer systems and case notes where necessary. If concordance between the number of cases submitted to REDCap and those identified independently is <90%, the Unit's data will be excluded from the final data analysis. This is consistent with quality assurance procedures used in other collaborative audit projects [25].

8. Data management and storage

Data collection will occur in accordance with the revised Caldicott principles of 2013 ("Caldicott 2"). Data for each patient will be anonymised using a unique alphanumeric study identification number. Participating units will be asked to securely store a local spreadsheet

linking study identification number with NHS number. No patient identifiable data will be centrally submitted or stored for the purposes of this audit.

Study data will be collected and managed using the REDCap electronic data capture tools. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research purposes. It provides:

- An intuitive interface for validated data entry
- Audit trails for tracking data manipulation and export procedures
- Automated export procedures for seamless data downloads to common statistical packages
- Procedures for importing data from external sources

9. Sample size and data analysis

All data analysis will occur centrally. It will be led and directed by the NeST Study Steering Group, with support from statisticians and methodologists within Queen's University Belfast.

9.1 Sample size

Data regarding the frequency of utilisation of NST in breast cancer is lacking. It is unclear what proportion of breast cancer patients are candidates for NST, and how often it is recommended by MDTs. It is anticipated that the majority of the 144 breast units within the UK are likely to consider this as a treatment option for their patients, although it is also likely that there is significant variation in its utilisation across the country. Based on previous experience with prospective collaborative studies such as the iBRA study, it is anticipated that approximately 40% of UK breast units may choose to participate in the audit. In order to obtain a representative picture of current UK practice, we therefore estimate that it will be necessary to run the audit prospectively for a minimum period of 6 months.

9.2 Data analysis

Simple summary statistics will be calculated for appropriate variables, including demographic data, treatment frequencies and durations and for surgical outcome measures (including mastectomy rates and surgical downstaging rates). Data will be tested for distribution and differences between groups using appropriate statistical techniques. Summary statistics will be calculated for each participating Trust and fed back to allow individual units to carry out comparisons with national practice.

10 Publication and authorship policy

The NeST Study Steering Group will be responsible for drafting manuscripts and preparing them for publication.

All publications from this project will be "on behalf of the Neoadjuvant Systemic Therapy in Breast Cancer (NeST) Study Group and the Mammary Fold Academic and Research Collaborative".

The International Committee of Medical Journal Editors (ICMJE) criteria (www.icmje.org) for authorship is based on the following four criteria:

1. Substantial contribution to the conception or design of the work; or the acquisition, analysis or interpretation of the data for the work and
2. Drafting the work or revising it critically for important intellectual content and
3. Final approval of the version to be published and
4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

The ICMJE states '*when submitting a manuscript authored by a group, the corresponding author should specify the group name if one exists and clearly identify the group members who can take credit and responsibility for the work as authors. The byline of the article identifies who is directly responsible for the manuscript and MEDLINE lists authors whichever*

names appear on the byline. If the byline includes a group name, MEDLINE will list the names of individual group members who are authors or who are collaborators, sometimes called non-author contributors, if there is a note associated with the byline clearly stating that the individual names are elsewhere in the paper and whether those names are authors or collaborators.'

All citable collaborators will therefore be listed at the end of the paper and their roles identified.

10.1 Criteria for citable collaborators status

Citable collaborators will have been required to make considerable contribution to the study. These will include leads at each unit and other team members (including consultant surgeons, SAS doctors, clinical nurse specialists or research nurses) who have recruited at least five patients to the study. Recruitment in this context includes the submission of ***at least five completed data sets***. Judgement may be used to determine participation according to local centre practice. Unit leads will be asked to provide details of their local team and whether individuals fulfil the criteria for citable or acknowledged collaborator status.

10.2 Acknowledged collaborators

Acknowledged collaborators will include consultant surgeons who contributed patients to the audit, but did not personally collect data and trainees who have made a lesser contribution to patient recruitment and data collection than that required for citable collaborator status. Trainees who are acknowledged contributors will also receive a certificate of participation for inclusion in their portfolios.

Local collaboratives and hospital Trusts will have ownership of their own data and will be able to present it locally if they wish.

11 Research governance

The main aim of the audit is to determine the practice and principal outcomes in relation to the use of neoadjuvant systemic therapies in the treatment of breast cancer. Data will be analysed at the conclusion of the study period to determine uptake of NST, response rates and surgical outcomes. Data for individual centres will be evaluated, compared with the national measures and fed back to individual participating units.

12 Study management

The study will be overseen by the NeST Study Steering Group, which will be constituted of breast surgeons and surgical trainees, medical oncologists (including trainees) and patient representation. There will be members with expertise in statistical methodology and study management. The Steering Group is expected to meet twice annually over the course of the study, although may meet more frequently if required. It is anticipated that the majority of the study workload and administration can be carried out as a "virtual group", by means of electronic communication

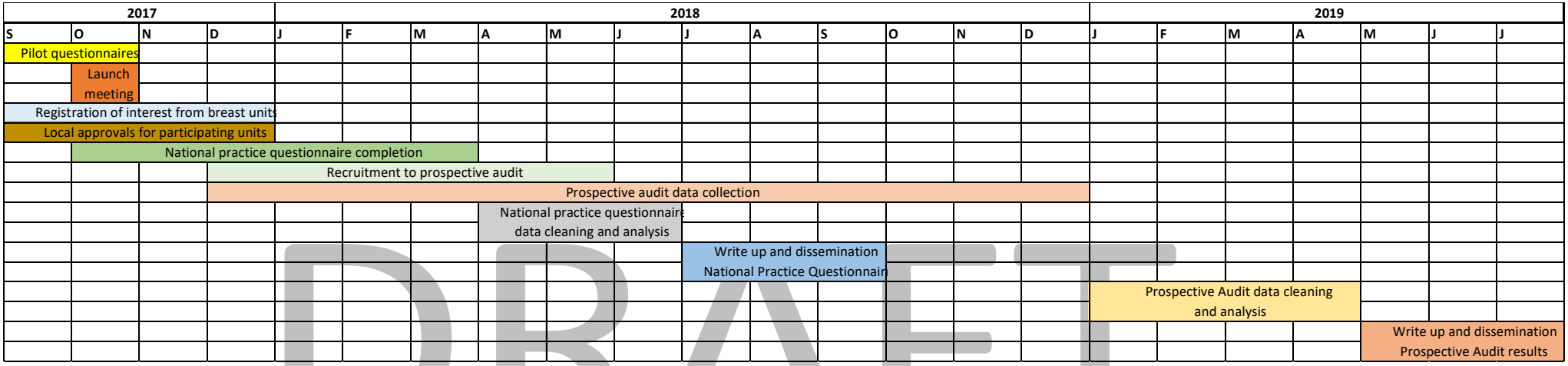
13 Study timelines

The following study timeline is proposed:

- Pilot study questionnaires
    - September - October 2017
- Study launch meeting
    - October 2017
- Registration of interest from breast units
    - September - December 2017
- Local approvals from participating units
    - September - December 2017
- National practice questionnaire completion

    - October 2017 - March 2018
- Patient recruitment to prospective audit
    - Patients with pre-operative MDT date between 1st December 2017 - 30th May 2018 inclusive
- Data collection period
    - 1st December 2017 - 31st December 2018 to allow sufficient time for completion of chemotherapy and surgical treatment
- Closing data for data submission
    - 31st January 2019
- Data analysis
    - National Practice questionnaire
        - 1st April 2018 - 30th June 2018
    - Prospective Audit data
        - 1st February 2019 - 30th April 2019
- Write up and dissemination
    - National practice questionnaire
        - July - September 2018
    - Prospective Audit data
        - May - July 2019

Gantt chart for NeST Study



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Appendix A: NeST Current Practice Questionnaire

Appendix B: NeST Prospective Audit Questionnaire